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Through,

1. Prof. Jagadeesh Prasad
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2. The Chairperson
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Respected Sir,

Sub: Submission of final-synopsis reg.

Ref: MU/EXB/Ph.D./CR.12/Chem/2022-23/E.25 Dated 19.04.2022

Inviting reference to the above, I am submitting herewith twelve copies of the final-synopsis of my Ph.D. thesis entitled "**Synthesis of Heterocycles using Iodine Reagents and Biological Studies of some Pentoxifylline Derivatives**" for the degree of Doctor of Philosophy in Chemistry. I request you to kindly do the needful and oblige.

Thank you, Yours faithfully,

(Mohankumar D)

Forwarded with the recommendation to the Chairperson, Department of Chemistry, Mangalore University for onward transmission to the Registrar (Evaluation), Mangalore University.

Date: 02-12-2024
Place: Mangalagangothri

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Title of the thesis: **Synthesis of Heterocycles using Iodine Reagents and Biological Studies of some Pentoxifylline Derivatives**

Name of the Institution: Department of Chemistry, Mangalore University

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Registration No & Date: MU/EXB/Ph.D./CR.12/Chem/2022-23/E.25 Dated 19.04.2022

Registration date: 09-09-2019

SYNTHESIS OF HETEROCYCLES USING IODINE REAGENTS AND BIOLOGICAL STUDIES OF SOME PENTOXIFYLLINE DERIVATIVES

Final-Synopsis

OF THE Ph.D THESIS SUBMITTED

TO

MANGALORE UNIVERSITY

FOR THE AWARD OF THE DEGREE OF

DOCTOR OF PHILOSOPHY

In

Chemistry

BY

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DECEMBER-2024

Final-synopsis

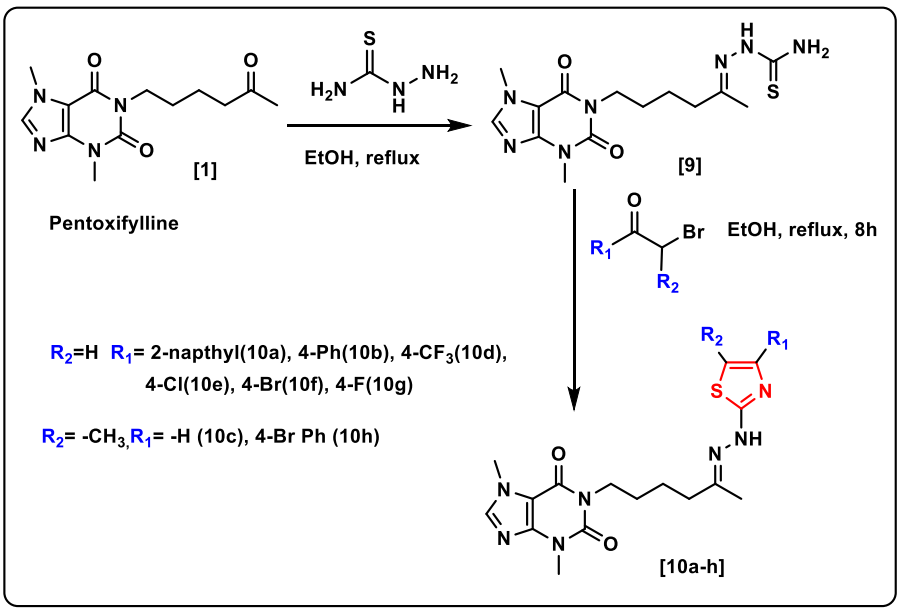
Chapter No	Title
1	Synthesis, characterization and antimicrobial activity studies of aryl thiazoles containing pentoxifylline
2A	Literature review on iodine reagents catalyzed sp^3 C-H functionalization of aryl methyl ketones
2B	Metal-free C-H functionalisation of imidazo[2,1-*b*][1,3,4]thiadiazoles: A Novel approach to bridgehead heteroaryl-1,2-diketones using Iodine /DMSO
3	$KI/K_2S_2O_8$ mediated oxidative C=C bond cleavage of N, N-dimethyl enaminones: A Facile approach for the synthesis of α-hydroxy acetophenones and synthetic applications towards the regioselective synthesis of the 2,5-disubstituted imidazoles and oxazoles.
4A	Iodine/DMSO promoted oxidative annulation of L-phenylalanine with aryl methyl ketone; An Easy approach for chemoselective synthesis of 2,3,5-trisubstituted pyridines
4B	Iodine/DMSO promoted [2+3] oxidative annulation of L-phenylalanine with aryl methyl ketones; A Facile approach for the synthesis of 2,5-disubstituted oxazoles
5	PIDA mediated oxidative [3+1+1] annulation of aryl methyl ketone; A Facile approach for the chemoselective synthesis of 5-substituted oxazoles

Chapter-1

Synthesis, characterization and antimicrobial activity studies of aryl thiazoles containing pentoxifylline

Pentoxifylline is a xanthine derivative and it is well known for its actions in peripheral vascular diseases,[1] human sperm motility enhancement[2] and other biological, pharmacological functions.[3-5] Among heterocyclic compounds, thiazole is a five-member unique heterocyclic motif containing sulfur and nitrogen. It posesse a broad range of biological activities and is found in many potent biologically active molecules and drugs such as sulfathiazole (antimicrobial drug), ritonavir (antiretroviral drug), abafungin (antifungal drug) and tiazofurin (antineoplastic drug).[6] Recently, thiazole-containing compounds have been successfully developed as possible inhibitors of several biological targets, including enzyme-linked receptor(s) located on the cell membrane.[7]

We intended to modify pentoxifylline by inserting an aryl thiazole ring and screening for the antimicrobial activity. Accordingly, a series of aryl thiazoles containing pentoxifylline were synthesized and characterized using ^{1}H-NMR, ^{13}C-NMR and LCMS spectral techniques. All the compounds were screened for their antibacterial activity against six different bacterial strains using Ampicillin, Streptomycin and Tetracycline as standards. We carried out the antifungal activity studies against four different fungal strains using Nystatin as standard. Among them, 10b, 10e and 10g showed very good antibacterial and antifungal activities almost equal to standard drugs.



Scheme-1. Synthesis of aryl thiazole ring containing pentoxifylline

CHAPTER-2 Section-A

Literature review on iodine reagents catalyzed sp^3 C-H functionalization of aryl methyl ketones

Transition metal and iodine reagents have been employed in sp^3 C-H functionalization of aryl methyl ketones for the synthesis of different synthetic intermediates and novel heterocyclic derivatives. C-H functionalization is an effective and powerful tool in synthetic chemistry for the direct synthesis of targeted functionalized molecules with good stereoselectivity[8] compared to multistep synthesis. It involves mild reaction conditions, atom and step economy and produces a very good to moderate percentage yield.

Transition metal salts like Cu(II),[9] Ni(II),[10] $Pd(OAc)_2$,[11] $Sc(OTf)_3$,[12] etc., were used in directed group-assisted C-H functionalization of inactive aliphatic and aromatic C-H bonds with good regioselectivity. Oxidants like TBHP,[13] Oxone,[14] NCS,[15] persulfate salts,[16] O_2[17] etc., promote the oxidative C-H functionalization of sp^2 and sp^3 C-H bonds. Electrochemical methods[18], mechanochemical grinding methods, [19] photocatalyzed visible light-mediated methods are other protocols for the C-H activation.[20]

Iodine reagents such as molecular iodine, TBAI and PIDA were used for the C-H functionalization of aryl methyl ketones to synthesize different synthetic intermediates, bioactive and pharmacologically important heterocycles. Iodine/DMSO is a versatile and efficient oxidant system for sp^3 C-H functionalization of aryl methyl ketones.[21] The reaction proceeds *via* iodination at the sp^3 C-H bond followed by nucleophilic attack by DMSO, Finally converts acetophenone into respective aryl glyoxal with loss of HI. This aryl glyoxal can be utilized for the synthesis of different heterocycles and synthetic intermediates efficiently stereoselectivity.

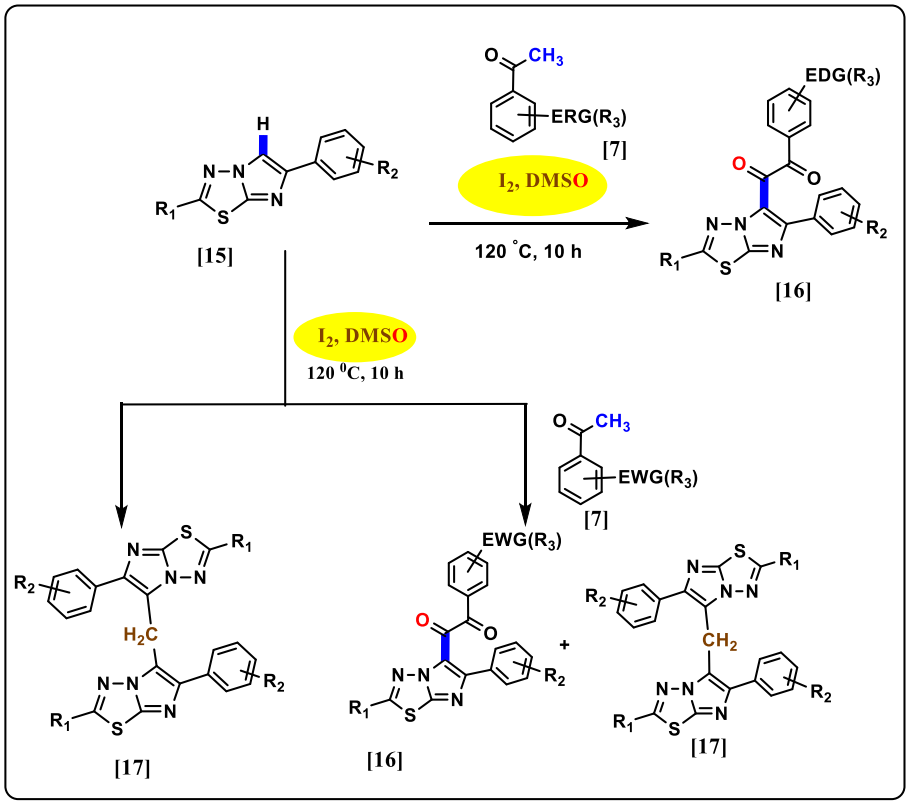
CHAPTER-2 Section-B

Metal-free C-H functionalisation of imidazo[2,1-*b*][1,3,4]-thiadiazoles: A novel approach to bridgehead heteroaryl-1,2-diketones using iodine /dmso

[1,3,4]-thiadiazole is a five-member heterocyclic ring bearing two nitrogen and one sulfur atoms. It is a very weak base and resistant to electrophilic substitution reactions because of the inductive effect of two nitrogen and sulfur atoms. Different methods have been developed to construct a variety of biologically and pharmacologically important compounds. [1,3,4]-thiadiazole derivatives exhibit a broad range of biological activities such as antimicrobial, anticancer, antioxidant, anti-inflammatory, and antihypertensive activity.[22]

Previous reports described the synthesis of the 1,2-diketones from alkene,[23] alkyne,[24] aryl methyl ketone[25] and α,β unsaturated ketone[26] under different metal-catalyzed and metal-free reagents promoted conditions.

Iodine/DMSO promoted oxidative dehydrogenative cross-coupling of imidazo[2,1-*b*][1,3,4]thiadiazole with different aryl methyl ketones to construct heteroaryl-1,2-diketones in good to high yield. This reaction features mild reaction conditions, metal-free, peroxide-free and less toxic reagents. In the absence of aryl methyl ketones methylene bridged *bis*-imidazo[2,1-*b*][1,3,4]-thiadiazoles were obtained with moderate yield. When electron-donating groups were present in the aryl methyl ketones an increase in the yield of heteroaryl 1,2-diketone was observed. When aryl methyl ketones had electron-withdrawing substituents, the formation of both heteroaryl 1,2-diketone and methylene bridged *bis*-imidazo[2,1-*b*][1,3,4]thiadiazole were observed.



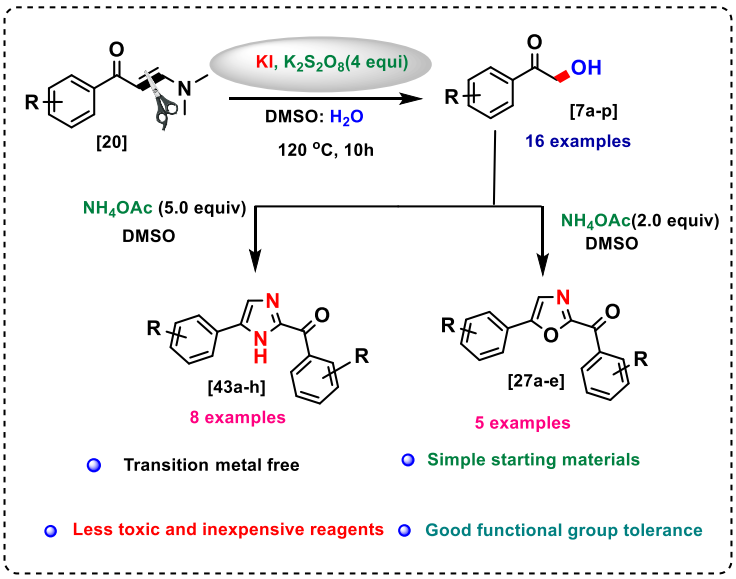
Scheme-2. Iodine/DMSO promoted C-H functionalization of imidazo [2,1-*b*][1,3,4]-thiadiazoles

Chapter-3

KI/$K_2S_2O_8$ mediated oxidative C=C bond cleavage of N, N-dimethyl enaminones: A facile approach for the synthesis of α-hydroxy acetophenones and synthetic applications towards the regioselective synthesis of the 2,5-disubstituted imidazoles and oxazoles

Structurally α- hydroxyl carbonyl compounds extend their applications in pharmaceutical, and material chemistry,[27] as templates in asymmetric catalysis[28] and as intermediates for various synthetic conversions.[29-31] α-hydroxy carbonyl compounds can be synthesized from alkene,[32] propargylic alcohol,[33-34] α-halo ketone[35] and α-substituted carbonyl compound[36-38] under different reagents and conditions. Previous reports are available on C=C bond cleavage of enaminones for the synthesis of α-C-H functionalized ketones.[39]

This chapters describes a chemoselective synthesis of α- hydroxy carbonyl compounds from simple N,N dimethyl enaminones. This reaction proceeds by persulfate-mediated oxidative C=C bond cleavage of enaminones by a free radical mechanism in the DMSO/H_2O solvent system.[40] This approach involves transition metal-free, ligand-free, additive-free, mild reaction conditions, inexpensive reagents, short reaction time and has good substrate scope. N-arylenaminones and enaminones of α-substituted ketones were unsuccessful for this transformation. Totally sixteen α-hydroxy acetophenones have been synthesised. Synthesized hydroxy ketones were used for the one-pot regioselective synthesis of 2,5-disubstituted imidazoles and oxazoles in good yield by using NH_4OAc as a nitrogen source.[41]



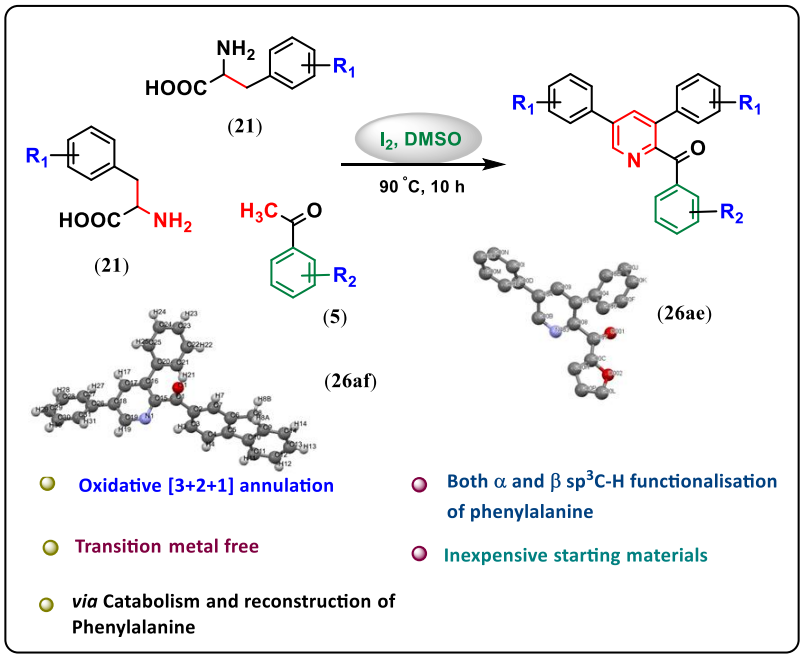
Scheme-3. KI/$K_2S_2O_8$ mediated synthesis of α-hydroxy acetophenones from N,N-dimethyl enaminones

Chapter-4A

Iodine/DMSO promoted oxidative annulation of l-phenylalanine with aryl methyl ketone; An easy approach for chemoselective synthesis of 2,3,5-trisubstituted pyridines

Pyridine derivatives exhibit a broad range of applications in the field of drug discovery,[42-43] material chemistry[44] and electrochemistry.[45] Recent reports revealed the construction of substituted pyridine derivatives using different metal salts and oxidants promoted C-H functionalizations.[46-47] Some of the previous reports described the synthesis of different heterocycles such as trisubstituted quinolones,[48] 2,5-disubstituted oxazoles and substituted pyridine[49] from L-phenylalanine.

Making use of catabolism and reconstruction properties of amino acids in the Iodine/DMSO oxidant system, we have developed an efficient protocol for the synthesis of 2,3,5-trisubstituted pyridine by oxidative cross-trimerisation of L-phenylalanine with aryl methyl ketone. This strategy involves metal-free, user-friendly, less toxic nitrogen source and easily available starting materials. Totally twenty-six compounds have been synthesized and were characterized by ^{1}H-NMR, ^{13}C-NMR and HRMS spectral techniques. The structures of 3,5-diphenylpyridin-2-yl)(furan-2-yl)methanone (**26ae**) and (3,5-diphenylpyridin-2-yl)(9H-fluorene-2-yl)methanone (**26af**) were confirmed by single crystal XRD.



Scheme-4. Oxidative annulation of aryl methyl ketone with L-phenylalanine for the synthesis of 2, 3, 5-trisubstituted pyridine

Chapter-4B

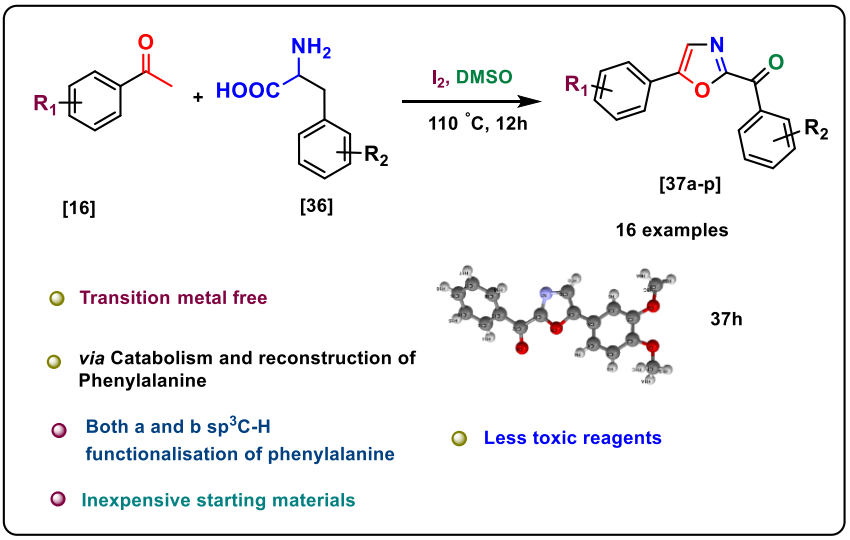
Iodine/DMSO promoted [2+3] oxidative annulation of l-phenylalanine with aryl methyl ketones; A facile approach for the synthesis of 2,5-disubstituted oxazoles

Oxazoles are five-member heteroaromatic compounds that are pharmacologically and biologically important scaffolds in drug design.[50-51]‘ Hinduchelins’ is a natural product containing oxazole ring which has potential iron cheating properties.[52] Oxazoles are capable of forming noncovalent interactions with a variety of enzymes and specific receptors leading to a wide range of biological activities such as antimicrobial,[53] antifungal,[54] antitubercular,[55] anticancer,[56] antimalarial,[57] antidiabetic,[58] anti-inflammatory,[59] ant1iviral,[60] cholinesterase inhibitors,[61] histone deacetylase inhibitor,[62] phosphodiesterase inhibitor.[63]

Most of the methods include the oxidation of oxazoline,[64] transition metal or metal-free oxidant catalyzed oxidative annulation of cyclic or acyclic precursors.[65] Previous methods for oxazole synthesis consist of expensive transition metal catalysts like $Pd(dba)_2$,[66] [Au][67] and oxidants, additives, ligands, and toxic starting materials like $TsCH_2NC$.[68] Most of the starting materials used are pre-functionalized, their synthesis increases the number of steps to achieve the targeted molecules. To replace the transition metal catalysts and increase the efficiency in functional group tolerance, significant demand exists to find interesting novel methodologies for the construction of oxazoles.

Here we are report the synthesis of 2,5-disubstituted oxazoles from simple aryl methyl ketones and L-phenylalanine in iodine/DMSO. L-phenylalanine undergoes catabolism *via* deamination and decarboxylation in the presence of iodine/DMSO, followed by the reaction with aryl glyoxal of aryl methyl ketone to give 2,5-disubstituted oxazole in good yield. $–CH_2-$ of phenylalanine undergoes oxidation to C=O in the same reaction condition. This reaction features transition metal-free, usage of less toxic, inexpensive reactants and reagents and good substrate scope with good yield. Totally sixteen new 2,5-disubstituted oxazoles have been syntheised and characterized by ^1H NMR, ^{13}C NMR spectroscopic techniques.

The structure of (5-(3,4-dimethoxyphenyl)oxazol-2-yl)(phenyl)methanone (**37h**) was confirmed by single crystal XRD. 2,5-disubstituted oxazoles were screened for their photophysical properties



Scheme-5. Chemoselective synthesis of 2,5-disubstituted oxazoles

Chapter-5

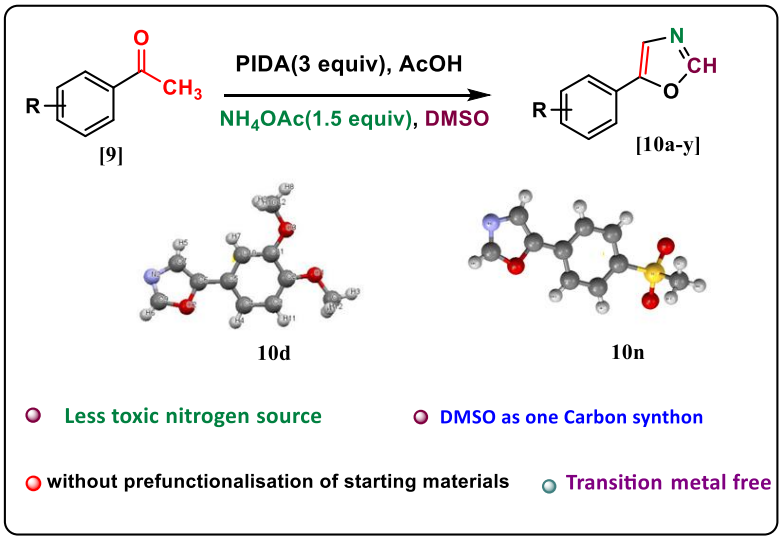
PIDA mediated oxidative [3+1+1] annulation of aryl methyl ketone; A facile approach for the chemoselective synthesis of 5-substituted oxazoles

Most of the available literature described the synthesis of disubstituted and multisubstituted oxazoles by using substituted alkene,[69] alkynes,[70] enaminones,[71] propargylamides,[72] aryl nitriles,[73] benzylamines,[74] acetophenones,[75] arylaldehydes[76] etc., as one of the starting material. However, only few reports are available for the synthesis of 5-substituted oxazoles. Recently reported methods describe the reaction of the aryl aldehydes with *p*-Toulenesulfonylmethyl isocyanides under different conditions like microwave irradiation,[77] ionic liquid mediated[78] and by using a strong base like n-BuLi.[79] Ling-Juan Zhang *et al*.,[80] have reported the copper-catalyzed synthesis of the 5-aryl substituted oxazoles from substituted pyruvic acids and *p*-tosyl methyl isocyanides in the presence of base KOH. However these methods have a few limitations like the usage of toxic starting materials like TosMIC and highly prefunctionalised starting materials like enamides, propargylamides increase the number of steps to achieve the synthesis of the substituted oxazoles.

We report herein a simple and efficient protocol for the chemoselective direct synthesis of the 5-substituted oxazoles *via* [3+1+1] annulation of simple and readily available acetophenones with NH_4OAc and DMSO using hypervalent (III)iodine (PIDA) as an effective oxidant. Here

PIDA plays a vital role in both sp^3 C-H functionalization of ketone and activation of DMSO by converting into methyl (methylene) sulfonium ion.[81] NH_4OAc and DMSO acts as one nitrogen and one carbon synthons respectively. Here new C-X (X=O, N) bond formations take place in a single step by employing less toxic reagents. This new approach has a wide substrate scope with good to excellent percentage yields. Totally twenty-five compounds have been synthesized. Structures of the two compounds 5-(3,4-dimethoxyphenyl)oxazole (**10d**) and 5-(methylsulfonyl)phenyl) oxazole (**10n**) were confirmed by single crystal XRD

All the synthesised compounds were characterised by ^1H NMR, ^{13}C NMR and LCMS/HRMS spectral techniques.



Scheme-6. Chemoselective synthesis of 5-aryl oxazoles

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